WO 2005/058910 PCT/CZ2004/000085

CLAIMS

1. The method of manufacturing of 7-ethyl-10-hydroxycamptothecin of formula I

HO
$$CH_3$$
 O CH_3 O CH_3

characterized in that 7-ethyl-1,2,6,7-tetrahydrocamptothecin of formula IV

is oxidized with an oxidizing agent selected from the group comprising iodosobenzene, an ester of iodosobenzene, sodium periodate, potassium periodate, potassium peroxodisulfate and ammonium peroxodisulfate, in a solvent formed by a saturated aliphatic monocarboxylic acid containing 1 to 3 carbon atoms, and in the presence of water.

2. The method according to claim 1, characterized in that the oxidizing agent is an ester of iodosobenzene.

3. The method according to claim 2, characterized in that the ester of iodosobenzene is an ester of iodosobenzene of general formula V

$$OR^1$$
 OR^1
 (V)

wherein substituents R^1 are the same or different and designate hydrogen, $-C(O)-R^2$ or $-SO_2-R^3$ where R^2 and R^3 independently are selected from a group comprising an optionally substituted alkyl group having 1 to 6 carbon atoms, an optionally substituted cycloalkyl group having 3 to 8 carbon atoms, an optionally substituted aryl group having 6 to 12 carbon atoms, and an optionally substituted aralkyl group wherein the aryl moiety has 6 to 12 carbon atoms and the alkyl moiety has 1 to 4 carbon atoms, with the proviso that at least one of the substituents R^1 is not the hydrogen atom.

- 4. The method according to claims 1 to 3, characterized in that the oxidizing agent is an ester of iodosobenzene selected from the group comprising iodobenzene diacetate, iodobenzene bis(trifluoroacetate) and hydroxy(tosyloxy)iodobenzene.
- 5. The method according to claims 1 to 4, characterized in that the oxidizing reagent is iodobenzene diacetate in an amount of 0.99 to 1.85 mol, preferably 1.28 to 1.56 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.
- 6. The method according to claim 1, characterized in that the solvent is acetic acid, formic acid or trifluoroacetic acid.
- 7. The method according to claim 6, characterized in that the solvent is acetic acid in an amount of 668 to 1001 mol, preferably 751 to 918 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.

WO 2005/058910 PCT/CZ2004/000085

8. The method according to claims 1 to 7, characterized in that water is used in an amount of 0.98 to 1.88 mol, preferably 1.28 to 1.58 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.

- 9. The method according to claim 1, characterized in that the oxidation is carried out at a temperature from 15 to 30 °C, preferably at 18 to 25 °C.
- 10. The method according to claim 1, characterized in that the oxidation is performed for 5 to 30 minutes, preferably for 10 to 15 minutes.
- 11. The method according to claim 1, characterized in that the starting 7-ethyl-1,2,6,7-tetrahydrocamptothecin is obtained by hydrogenation of 7-ethylcamptothecin of formula II

in a saturated aliphatic monocarboxylic acid having 1 to 3 carbon atoms, using hydrogen in the presence of a hydrogenation catalyst and a sulfur compound that partly deactivates the hydrogenation catalyst.

12. The method according to claim 11, characterized in that the saturated aliphatic monocarboxylic acid is formic acid, acetic acid or trifluoroacetic acid.

WO 2005/058910 PCT/CZ2004/000085

- 13. The method according to claim 12, characterized in that acetic acid is used in an amount of 791 to 1187 mol, preferably 890 to 1088 mol, per 1 mol of 7-ethylcamptothecin.
- 14. The method according to claim 11, characterized in that the sulfur compound that partly deactivates the hydrogenation catalyst is dimethyl sulfoxide.
- 15. The method according to claim 14, characterized in that dimethyl sulfoxide is used in an amount of 0.18 to 0.33 mol, preferably 0.23 to 0.28 mol, per 1 mol of 7-ethylcamptothecin.
- 16. The method according to claim 11, characterized in that the hydrogenation catalyst is a noble metal.
- 17. The method according to claim 16, characterized in that the noble metal is platinum.
- 18. The method according to claim 17, characterized in that platinum is used on an activated carbon or aluminum oxide carrier.
- 19. The method according to claim 18, characterized in that platinum is used in an amount of 0.018 to 0.027 mol, preferably 0.020 to 0.025 mol, per 1 mol of 7-ethylcamptothecin, in the form of a hydrogenation catalyst, formed by platinum on an activated carbon with platinum content 5 %.
- 20. The method according to claim 11, characterized in that the hydrogenation is carried out at a pressure from 0.3 to 0.7 MPa, preferably at a pressure from 0.4 to 0.6 MPa.

21. The method according to claim 11, characterized in that the hydrogenation is carriet out at a temperature from 45 to 85 °C, preferably at 58 to 72 °C.

22. The method according to claim 11, characterized in that the hydrogenation is carried out for 24 to 70 hours, preferably for 40 to 50 hours.